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ORAL ADMINISTRATION OF PENICILLIN*

Its Use in One Hundred and Fifty Cases

Sidney Ross, M.D., Frederic G. Burke, M.D., and Sidney Olansky, M.D.

The rôle of penicillin administered by mouth has been reported on by several investigators,[1–6] and the conclusion seems warranted that if the drug is given in sufficiently large doses, cures may be expected in susceptible infections. The optimal dose, as well as the necessity of preliminary or concurrent neutralization of the gastric acidity to avoid the inactivating influence of hydrochloric acid in the stomach when penicillin is administered orally, has been the subject of some controversy in the recent literature.[2–4, 7] To evaluate the latter point, penicillin blood levels were determined in a control group of over 600 subjects, plain calcium penicillin tablets containing a binding substance but without incorporated antacid, calcium penicillin tablets containing calcium carbonate, sodium citrate incorporated as buffers and plain calcium penicillin tablets with simultaneous administration of benzoic acid being used; the last combination was based on a report that benzoic acid is conjugated with glycine to produce para-aminohippuric acid and in this form competes with penicillin for excretion in the urine, thus prolonging and increasing the blood penicillin concentrations.[8]

The resulting penicillin blood levels at different intervals following the administration of these various preparations, details of which will be presented more fully elsewhere, indicated that incorporation of a buffer such as calcium carbonate or sodium citrate in commercial penicillin tablets does not represent a necessary adjunct to oral penicillin therapy and that the blood levels obtained are not materially affected when these antacids are omitted. This is in keeping with the conclusion of McDermott et al.[9] that penicillin preparations based solely on protection from acid destruction are not superior to penicillin alone. Similarly, benzoic acid did not produce an increase or prolongation of the blood level when administered simultaneously with oral penicillin. Another point emphasized by this study was the noticeable variation in the blood levels achieved with the same oral dose of penicillin in different subjects; there also was considerable variation in the blood concentrations in the same subject from time to time when the same oral dose was employed. The penicillin titer in a given person was thus found to be somewhat unpredictable after oral administration. When the dose of oral penicillin was doubled or quadrupled, a comparable increase in the blood level did not result.

* Summary of an article which appeared in the New England Journal Med., **236:** 817 (May 29) 1947.

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In the present series penicillin was administered orally in a total of 150 cases, including gonorrhea, subacute bacterial endocarditis, pneumonia, syphilis, cellulitis, impetigo and streptococcal pharyngotonsillitis. There were 76 children and 74 adults. Plain calcium penicillin tablets without incorporated antacid, containing 25,000 units were employed in the treatment of 130 cases, and in five cases, tablets buffered with sodium citrate† were used. In the other 15 cases a double gelatin capsule containing 100,000 units of penicillin was administered.

TABLE 1

RESULTS OF ORAL ADMINISTRATION OF PENICILLIN IN THE TREATMENT OF GONORRHEA

TYPE OF DISEASE	FORM OF DRUG	TOTAL DOSAGE	DURATION OF THERAPY	CURES	FAILURES	POSSIBLE REINFECTIONS
		Oxford units	*hr.*			
Acute gonococcal urethritis	Tablet	300,000 (50,000 every 3 hours)	15	49	1	1
	Capsule	300,000 (50,000 every 3 hours)	6	1	1	
Acute gonococcal vulvovaginitis	Capsule	300,000 (100,000 every 3 hours)	6	1	1	
	Capsule	400,000 (100,000 every 3 hours)	9	9		
	Tablet	300,000 (50,000 every 3 hours)	15	7	4	
	Tablet	300,000 (50,000 every 4 hours)	28	10	2	
	Tablet	200,000 (25,000 every 4 hours)	28	5	2	
	Tablet	500,000 (50,000 every 3 hours)	36	1		1
Totals				83	11	2

CLINICAL RESULTS

Gonorrhea

A total of 96 patients with gonorrhea were treated with penicillin by mouth. Of these, 63 were adults and 33 were children ranging in age from three to nine years (Table 1). In the adult group an arbitrary dosage schedule of 50,000 units of penicillin was administered every three hours for six doses, or a total of 300,000 units. The duration of therapy between

† Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

the first and last dose was thus fifteen hours. The diagnosis was established prior to the institution of therapy by the demonstration of the organism on culture as well as on smear. Of the 63 cases treated, 57 were cured, and 5 were failures. One patient who had had negative cultures following therapy returned a month later with a recurrence of the urethral discharge. He had had several sexual exposures during this hiatus, and this recurrence probably represented a reinfection rather than a relapse. Among the 51 men in the group there was only one failure, whereas among the 12 women there were 4 failures, 2 of which occurred in pregnant women.

Of the 33 children all were girls except one. The total dosage employed ranged between 200,000 and 500,000 units, the majority (24 patients) receiving either 300,000 or 400,000 units. There were failures in 5 cases. The gonorrheal discharge usually disappeared in eight to twenty-four hours.

In a total of 96 cases there were failures in 11—a recovery rate of 89 per cent—with the use of at least 300,000 units (50,000 units every three or four hours) in over three fourths of the patients treated. The results are comparable to those obtained when approximately 100,000 to 150,000 units of penicillin is injected intramuscularly. The fact that 10 failures occurred in female patients is in keeping with the premise that the criteria as well as the achievement of cures of gonorrhea may be somewhat more difficult in females than in males when oral penicillin is employed. Regarding the optimal dose of oral penicillin in the treatment of gonorrhea, no categorical statement is possible until a greater number of cases have been treated.

It is important to emphasize the fact that the indiscriminate use of oral penicillin in the treatment of gonorrhea without adequate supervision should be discouraged. All patients should be serologically tested for syphilis prior to the institution of therapy, and the tests should be repeated at monthly intervals for three months to avoid the possibility of giving subcurative doses to those with associated syphilis.

Subacute Bacterial Endocarditis

It was deemed of some academic interest to attempt to treat a case of subacute bacterial endocarditis with penicillin administered orally when the organism was relatively sensitive. The case summary is as follows:

M. P., an 11-year old girl, was seen on April 4, 1945, when a diagnosis of interventricular septal defect and probable subacute bacterial endocarditis was made. She was admitted to the hospital on the same day.

A heart murmur had first been noted when the patient was 1½ months old. Cyanosis and dyspnea had not been present at any time. Development had been normal, and the past history was essentially irrelevant.

Four weeks prior to admission she complained of easy fatigability and copious night sweats; a persistent fever with daily temperature elevations was observed.

Physical examination revealed a well developed and well nourished girl who appeared pale but not acutely ill. No petechiae were noted. The second left upper molar tooth was decayed and loose. A harsh loud systolic murmur with maximum intensity in the 3rd and 4th interspaces about 2 cm. to the left of the sternum was present and was transmitted over the entire precordium. There was an intense systolic thrill in the area where the murmur was loudest. The spleen was not palpable, and the remainder of the physical examination was negative. The temperature was 103°F., the pulse 128, and the respirations 27. An electrocardiogram was normal. A roentgenogram of the chest showed moderate enlargement of the right and left ventricles.

Three cultures taken on April 21, 22 and 24, respectively, showed the presence of thirty, forty-four and twelve colonies of Streptococcus viridans per cubic centimeter of blood. The strain showed a sensitivity range to penicillin of from 0.05 to 0.1 Florey units. Repeated sedimentation rates ranged between 30 and 45 mm. per hour (Wintrobe), and a hemogram showed evidence of a moderate degree of anemia.

The temperature during the first 2 weeks under observation showed a daily rise between 100 and 103.4°F. Specific therapy was started on April 29. Sodium penicillin was prepared in double gelatin capsules, and 100,000 units was given every 3 hours. The patient was given a soft, fat-free diet with moderate limitation of fluids, and the feeding schedule was slightly changed so that at no time was penicillin given simultaneously with a meal. Eight hours after the initiation of oral penicillin the temperature fell from 102°F. to normal and remained normal thereafter except for a transient rise to 100°F. on the 9th day, at the time of the extraction of the decayed tooth.

A blood culture obtained 12 hours after the start of treatment showed no growth, and daily blood cultures taken during the entire period of 2 weeks during which the patient received penicillin were negative. Penicillinase was added to the broth in one of the cultures, and no growth was observed.

The patient received 100,000 units of penicillin as a single dose every 3 hours for 14 days—a total dose of 11,300,000 units. No toxic symptoms were observed. White-cell counts made every other day were normal; the sedimentation rate, however, remained moderately rapid. Five blood transfusions of 250 cc. were given over a period of 2 weeks to combat the anemia.

The patient was observed in the hospital for an additional 9 days after

penicillin had been discontinued; blood cultures during that period were negative. She was discharged on May 21 and was examined every 2 weeks for the ensuing 12 months. The child was given complete freedom in her range of activity except for the avoidance of exhaustive play. The daily temperature reading was recorded. She remained entirely afebrile, numerous blood counts were normal and blood cultures taken at frequent intervals during the follow-up period remained consistently sterile. She gained 15 pounds in weight. A roentgenogram showed no change in the cardiac dimensions.

Another patient with subacute bacterial endocarditis due to Str. viridans superimposed on a congenital cardiac defect was similarly treated for a month, during which 20,000,000 units was administered. Blood cultures, however, remained positive intermittently during that interval, and after what was considered a fair trial, the oral method of administration was abandoned and the intramuscular route was initiated.

In spite of the striking results obtained with the oral administration of penicillin in one of these cases, subacute bacterial endocarditis is of such gravity that the use of the oral route in this disease is not recommended. Undoubtedly, cures could be obtained in some cases, but parenteral administration offers a more reliable mode of therapy and is the treatment of choice.

Pneumonia

A series of 17 cases of pneumonia were treated with oral penicillin. Of these, 12 occurred in children varying in age from three to twelve years, whereas the remainder were in adults. A pneumococcus was isolated in 9 cases in the pediatric age group, and a hemolytic streptococcus was the causative organism in the other 3. The 5 cases in adults were due to pneumococcus, and in 2 of these positive blood cultures were obtained. Penicillin sensitivity determinations were not done. In all cases the patients were mildly to moderately ill prior to the initiation of therapy.

The usual dosage was approximately 50,000 units every three hours in 15 cases and 100,000 units every three hours in the other 2 cases. Penicillin therapy was maintained usually for forty-eight to seventy-two hours after the temperature had returned to normal. The total oral dose varied between 500,000 and 2,000,000 units in 16 cases, and in the other case 8,000,000 units was used; the average dose in the 17 cases was 1,500,000 units.

With the exception of one patient, the duration of therapy varied between one and a half and seven days, with an average of four and a half days per patient. The temperature returned to normal by crisis usually within twelve to thirty-six hours after the initiation of therapy in 14 cases, and

prompt clinical improvement was observed. In no case was a recurrence of fever or leukocytosis, or both, following termination of therapy noted. There was no perceptible difference between the response of the adults and that of the children in this series.

In 3 cases the temperature came down by lysis during a period ranging from three to eight days, and slow resolution of the pneumonic process was observed, requiring six to twelve days. In one patient, an acutely ill eleven-year-old boy, pneumonia due to a Type 14 pneumococcus was complicated by an empyema at the time of admission. He received 480,000 units of penicillin orally every day, a total of 8,000,000 units being given for the eighteen-day interval during which therapy was maintained. In addition, 40,000 units of penicillin was injected into the pleural cavity on three alternate days. Recovery was gradual, the temperature slowly returning to normal by lysis over the course of eight days and the empyema subsiding.

The results obtained with penicillin administered orally in the treatment of pneumonia both in adults and in children indicate that, in the majority of cases, such therapy is efficacious if the drug given is in sufficiently large doses. The total dose used was approximately three to four times the parenteral dosage usually employed. The recommended dose must be predicated on the severity of the pneumonia at the time of admission; a schedule of 50,000 to 75,000 units every three hours for a total of 1,500,000 to 2,000,000 units, however, seemed to be adequate in the majority of cases, although it should be pointed out that two thirds of the patients were children. Pneumonia complicated by empyema is probably best treated by parenteral rather than oral administration of penicillin, together with intrapleural instillation of the drug.

Syphilis

Penicillin was administered orally in 3 adult cases of early syphilis. The dosage schedule consisted of 50,000 units of calcium penicillin in tablet form every four hours for twelve days, or a total of 3,600,000 units.

In one case the quantitative Kahn titer was 20 units prior to the initiation of therapy, and the serologic tests became negative within three months; a relapse occurred two and a half months later, however, and the serologic test was still positive after a seven months' follow-up period.

In the other cases, the quantitative serologic estimations were 120 and 260 Kahn units respectively prior to treatment, and in both cases the tests were negative after a six to eight months' follow-up period. One of these patient experienced a mild Herxheimer reaction.

In 10 other patients with syphilis, the lesions that had been dark-field

positive became dark-field negative within eighteen hours after the administration of 100,000 units of penicillin by mouth. Herxheimer reactions were noted in 3 cases. No attempt was made to treat the patients fully with penicillin by mouth, since the object of this preliminary trial was to determine the rapidity and the dose required to produce dark-field negativity.

In the 3 cases fully treated penicillin given orally produced serologic reversals with a total dose of 3,600,000 units. In 1 case, however, a relapse occurred within five and a half months, and the follow-up examination in the other 2 cases was too short to permit any statement regarding the permanency of the negative serologic tests obtained. It is possible that a total dose of 5,000,000 to 10,000,000 units is required in early syphilis if penicillin is administered orally.

In view of the several complexities in the management of a case of syphilis with penicillin and the relatively high percentage of relapses, the demonstration of serologic reversals with the oral administration of penicillin is probably of academic interest only, at least for the present, except in cases in which the patient is treated in a hospital and observed closely, with serial quantitative serologic examinations following termination of therapy. Unless it is rigidly controlled, such therapy introduces the additional hazard of attempts at self-medication and the administration of subcurative doses.

Miscellaneous Infections

Twenty-three cases of cellulitis in children ranging in age from three to eight years were treated with oral penicillin. The cellulitis involved various sites, some cases having associated abscess formation. A three-hour divided dosage schedule ranging from 25,000 to 50,000 units was employed, with the total dose varying from 240,000 to 1,110,000 units. Hot moist compresses were used concomitantly, and when fluctuation occurred, the area was incised and drained. The organism in the majority of cases in which pus was obtained was either hemolytic staphylococcus or streptococcus. The results paralleled those obtained with parenteral administration of penicillin when the drug was given in approximately one third to one fourth the oral dose.

Five cases of impetigo in infants ranging from two months to two years of age showed a prompt response within two to four days after the oral administration of penicillin varying in dosage from 400,000 to 900,000 units.

Four cases of acute pharnygotonsillitis due to a hemolytic streptococcus responded well to 800,000 units of penicillin administered orally on a dosage schedule of 50,000 units every three hours.

SUMMARY

Penicillin was administered orally in a total of 150 cases, including gonorrhea, subacute bacterial endocarditis, pneumonia, syphilis, cellulitis, impetigo and acute pharyngotonsillitis.

The commercial penicillin tablets used in this study were effective in penicillin-susceptible infections if given in sufficiently large doses.

The fundamental principles of penicillin therapy when the oral route is employed do not differ materially from those attendant on the parenteral administration except for the greater oral dose required.

In view of the relatively small number of cases, as well as the age range in this series, no categoric statement is possible regarding the optimal oral dose of penicillin. The dosage varies from case to case, depending on the severity and type of infection. The inadvisability of indiscriminate oral administration is emphasized.

REFERENCES

1. Burke, F. G., Ross, S., and Strauss, C.: Oral Administration of Penicillin; Preliminary Report. J. A. M. A., **128:** 83–86, 1945.
2. Ross, S., Burke, F. G., and McLendon, P. A.: Penicillin by Mouth: Report of Clinical Trial. J. A. M. A., **129:** 327–332, 1945.
3. Finland, M., Meads, M., and Ory, E. M.: Oral Penicillin. J. A. M. A., **129:** 315–320, 1945.
4. Cutting, W. C., Halpern, R. M., Syltan, E. H., Armstrong, C. D., and Collins, C. L.: Administration of Penicillin by Mouth; with Results in Treatment of Gonorrhea. J. A. M. A., **129:** 425–432, 1945.
5. Bunn, P. A., McDermott, W., Hadley, S. J., and Carter, A. C.: Treatment of Pneumococcic Pneumouia with Orally Administered Penicillin. J. A. M. A., **129:** 320–327, 1945.
6. Gyorgy, P., Vandegrift, H. N., Elias, W., Colio, L. G., Barry, F. M., and Pilcher, J. D.: Administration of Penicillin by Mouth; Preliminary Report. J. A. M. A., **127:** 639–642, 1945.
7. Seeberg, V. P., and Collen, M. F.: Calcium Carbonate as Antacid for Oral Penicillin. Science, **102:** 255–227, 1945.
8. Bronfenbrenner, J., and Favour, C. B.: Increasing and Prolonging Blood Penicillin Concentrations following Intramuscular Administration. Science, **101:** 673, 1945.
9. McDermott, W., Bunn, P. A., Benoit, M., Dubois, R., and Reynolds, M. E.: Absorption of Orally Administered Penicillin. Science, **103:** 359–361, 1946.

CHOLEDOCHUS CYST

Case Report No. 100

James Keating, M.D. P. C. 46-8774

Choledochus cyst is a true cyst of the common bile duct. It is a very rare condition and because of this, the diagnosis is seldom made. Judd and Greene reported that over a twenty year period, there were 17,381 operations performed on the biliary tract at the Mayo clinic and only once was a true cyst of the common duct encountered and it was present in a case in which cholecystectomy had been performed and stones found in the common duct. Levenson has reported that the first case of cyst of the common duct was that cited by Vater in 1723 and that Todd in 1817 reported another case; however the validity of these two cases has been questioned because in both cases there was present a scirrhous pancreatitis causing the obstruction. Zinninger and Cash in their review of the literature, collected and analyzed 109 reported cases. They accepted 82 as true cases and added one of their own. They did not include those cases caused by complete occlusion with stones, tumors, traumatic stricture, pancreatitis or complete atresia of the common bile duct in children.

REPORT OF A CASE

A two and one half month old white female was admitted to the Children's Hospital on September 26, 1946 because of persistent jaundice since birth. There was a history of a normal gestation period with no trauma or difficulty at birth and the mother's serology during pregnancy had been negative. The jaundice which was present at birth became worse at the end of one week and during the following days presented periods of definite remissions of the jaundice. The infant was breast fed for ten days following delivery and then she received a formula of evaporated milk which she would frequently vomit. The vomitus was never bile stained. Whole boiled milk was then tried and she seemed to handle it better although some vomiting persisted. She had been constipated since birth and her bowel movements appeared acholic and somewhat greasy. The urine was very yellow. The mother noted that the infant scratched herself quite often but at no time did she notice any change in the size of the abdomen, cyanosis or fever.

Physical examination on admission revealed a well developed and nourished two and one half month old white female who seemed alert and active. Her skin was jaundiced, dry and leathery and a few spider-like petechiae were noted. The lymph nodes were small and felt shotty. The

sclera was yellow. On palpating the abdomen, an orange-sized mass was noted which extended from the right upper quadrant almost down to the right iliac crest. It felt smooth and cystic. The liver was palpable one finger's breadth below the right costal margin.

Examination of the blood showed no abnormality except for a slight achromia and a macrocytosis. Blood Kahn and Mazzini tests were negative. Prothrombin time was 90% of normal, icterus index was 80 units, Van den Bergh was immediate and direct and the quantitative was 4.3 mgm. of bilirubin per 100 cc. Urine examinations were positive for bile and negative for urobilinogen. Repeated stool examinations for bile were negative. The cephalin flocculation test was negative in 24 hours and 2 plus in 48 hours. The blood type was A International, and the Rh blood factor was absent.

X-rays of the long bones taken on September 27, 1946 were indicative of a retardation of growth. A flat plate taken on the same date showed the intestines to be displaced away from the midline to the left by a mass in the right upper quadrant which extended across the midline and inferiorly to the region of the superior iliac crest. The mass was not believed to be connected to the liver but was thought to be in close relation to it. Its consistency was suggestive of a semi-cystic tumor. On September 30, 1946 after a barium meal an X-ray was taken and the stomach was found to appear normal and the intestines to be displaced toward the left. X-ray of the colon showed the distal one half to be displaced toward the left and downward. The mass in the right upper quadrant appeared posterior to the colon and displaced the latter to the floor of the pelvis. An intravenous pyelogram was essentially normal.

On October 5, 1946 a laporotomy was performed and a large choledochus cyst was found. The cyst was anastomosed with the jejunum, the inferior border of the cyst forming the anastomosis. The immediate post-operative condition was good but despite supportive measures of transfusions and clyses the infant's course was downhill. The abdomen became distended, the infant became cyanotic and on October 8, 1946 she expired.

NECROPSY SUMMARY

Dr. Lois Murphy: Post mortem examination revealed the cystic mass to be continuous with the biliary system and it contained dark green bile. The cyst was retroperitoneal and extended into the pelvis inferiorly; it displaced the liver upward until the dome of the right diaphragm was at the level of the third intercostal space. The cyst compressed the lower pole of the right kidney until the thickness of the parenchyma was one third that of the upper pole. On the left it extended slightly beyond the midline and distorted the normal distribution of the pancreas into separate

small masses of arc-shaped tissue which followed the course of the duodenum. The cystic mass showed the operative anastomosis with the terminal jejunum to be free from any leakage. The distal portion of the bowel contained bile stained material to a point 30 cm. from the ileocecal valve. The remaining ileum and colon were entirely collapsed. The

FIG. 1. The arrows point to the huge cystic mass arising from the common bile duct which almost approximates the liver in size. The dark piece of bowel lying next to the cyst is gangrenous, probably secondary to the attempted operative repair.

segment of bowel proximal to the anastomosis was dilated and discolored with some hemorrhagic areas. The duodenum was firmly attached to the left side of the cyst for a distance of 2 cm. The duct of Wirsung with its duodenal papilla and ampulla of Vater were identified and the pancreatic duct admitted a bristle. The cystic mass was identified as a greatly dilated common bile duct. The cystic duct was identified. The hepatic ducts

were all dilated well into the liver. No communication and no cord or remnant of any attachment between the duodenum and cyst could be found. On microscopic examination the liver was markedly cirrhotic, pigmented and the biliary capillaries were distended with biliary thrombi. The islets of the pancreas appeared enlarged and there was a generalized increase in fibrous tissue. The ducts were dilated and normal acini were absent. The lungs were edematous and showed a vascular congestion.

The pathological diagnosis was: 1) Choledochus cyst with occlusion at the ampulla of Vater; operative anastomosis of the cyst with terminal jejunum with partial secondary intestinal obstruction, 2) biliary cirrhosis, 3) pancreatic fibrosis and 4) pulmonary congestion.

DISCUSSION

James Keating, M.D.: Swartley and Weeder believe that a choledochus cyst is the result of faulty development and give the following explanations: 1) congenital malformation with congenital atresia of the common duct, 2) an abnormal course of the duct through the duodenum causing kinking and obstruction, 3) a valve-like fold at the mouth of the intraduodenal portion of the duct, 4) congenital narrowing of the wall due to the presence of infection, 5) congenital weakness of the wall of the duct, 6) a complication of pregnancy causing a twisting or kinking of the duct, 7) a primary congenital defect with modifying factors such as infection, spasm, kink, valves or atresia, 8) trauma, 9) pancreatic adenomas, 10) pressure on the common duct by enlarging tuberculous lymph glands. In their cases they believe two factors were responsible including congenital malformation and infection. The condition is generally thought to be congenital. Rostowzew believes that the cyst is a result of an abnormal course of the common duct through the wall of the duodenum and on several occasions it has been found that the end of the duct instead of entering the duodenum from right to left opens from the front backward. Levenson thinks that the angular insertion instead of being the cause is the result and that the underlying condition is the congenital weakness in the wall of the duct. This view is shared by Gross. Budde believes that the cysts are due to congenital dilation of the extraduodenal portion of the common duct which is increased by valvular obstruction at the lower end by inspissation of bile and suggested that the primary diverticulum is the result of a pancreatic rest in the wall of the common duct in which the cells break down and a dilatation of the duct follows. This hypothesis was based on the analogy of diverticulum of the duodenum which often contains pancreatic tissue.

Judd and Greene found in a review of 64 cases that 52 of the patients were females and 10 were males (in two cases the sex was not listed).

Swartley and Weeder found that it was more frequent in females, the ratio being 68 to 14. They found 28 cases from birth to ten years, 20 in those from 21 to 30 years, 7 in the age group 31 to 40 and 7 in those over 40 years of age. The average age of those reported by Judd and Greene was 15½ years. In their series they reported that most of the patients did not present themselves until after the symptoms had been present for 2 months to 36 years. Their youngest subject was an almost full term male fetus noted by Hellinger and the oldest was a woman aged 50 years observed by Reed and Burrell.

In the case reported the condition was present at birth. Judd states that in most cases which he reported, the symptoms appeared before the patients were ten years of age and that in many of them they were not older than 6 months. The oldest patient was 20 years of age before any symptoms were noted.

The usual symptoms are recurrent jaundice and/or pain in the region of the liver and a palpable tumor. In some cases there are acholic stools as in the case reported here but this is not a consistent finding in most cases because the cyst may drain periodically and bile may be found in the stools. Probably the most significant finding is the presence of a palpable tumor the size and consistency of which may vary depending upon its emptying ability. In reviewing the literature, jaundice was the most constant finding and its degree varied from a slight icteric tint to a severe icterus. It has been noted that the cyst may become larger and firmer after a meal probably due to the active secretion. Other symptoms that have been observed are nausea, vomiting, diarrhea and fever.

The diagnosis should be made more frequently in the future than it has been in the past. Of special importance in the diagnosis are jaundice, persistent or recurrent, especially in a young female, a cystic mass in the right upper quadrant, acholic stools and pain in the right upper quadrant. The differential diagnosis should include congenital atresia of the biliary ducts, cysts of the pancreas and mesentery, echinococcus cyst, hydrops of the gallbladder, retroperitoneal cysts, cysts of the liver, obstruction of the common duct by round worms or stones, ovarian cysts, hydronephrosis, cholecystitis, intestinal obstruction, catarrhal jaundice and perforation of the gallbladder.

X-ray findings in the case reported are typical of those described in the literature. Thomas described a fish-hook stomach which he was able to demonstrate by sagittal irradiation. He also described a semicircular depression of the greater curvature of the stomach with a transparent lumen in the region of the antrum and the parallel lines of the folds of the stomach when the ascending extremity of the stomach was pushed upwards and to the left.

The treatment of this condition is surgical with a preference to anastamosis of the cyst to the duodenum or a possible resection of the cyst with an end to end anastomosis of the resected duct. The mortality following external drainage has proved to be almost 100 percent. Marsupialization of the sac has been tried with very poor results. Swartley and Weeder found that the results of the various methods of treatment in 83 cases were as follows: 27 drained, 24 died; drainage with secondary anastamosis, 5 out of 14 died; excision of the cyst with anastamosis of the hepatid duct resulted in one death in the three cases in which it was tried; excision of the cyst with secondary anastamosis of the hepatic duct to the intestine was done successfully in one case reported; excision of the cyst without anastamosis was done six times with six deaths. These authors found that the mortality in all untreated cases, those aspirated alone and those excised without anastamosis was 100%; by drainage alone it was 88%; drainage with secondary anastamosis 35%, and primary anastamosis 28.9%. It is obvious from their report that primary anastamosis offers the best prognosis while choledochoduodenostomy is the procedure of choice.

The principal cause of death in the series reviewed by Judd and Greene was hemorrhage while peritonitis, exhaustion, cardiac failure, cholangitis and shock were listed as other causes.

BIBLIOGRAPHY

1. Judd and Greene: Surgery, Gynecology and Obstetrics. March, 1928, 317–323.
2. Thomas, Erich: Roentgen Diagnosis of so called Idiopathic Cyst of the Common Bile Duct. Zentralblatt fur Chirurgie, **54:** 2289–2292, Sept. 3, 1927.
3. Swartley and Weeder: Choledochus Cyst with a Double Common Bile Duct. Annals of Surgery, **101:** 912, March, 1935.
4. Zinninger and Cash: Congenital Cystic Dilatation of the Common Bile Duct. Arch. Surg., **24:** 77, 1932.
5. Boehm: A Case of Congenital Atresia of the Bile Duct. Ztschr. f. ang. Anat. and Konstitutionslehre, **1:** 109, 1913.
6. Lange, Kurt: Idiopathic Cyst of the Bile Duct. Zentralblatt fur Chirurgie, **54:** 2287–2289, Sept. 3, 1927.

VITAMIN ADVERTISING AND THE MEAD JOHNSON POLICY

The present spectacle of vitamin advertising running riot in newspapers and magazines and via radio emphasizes the importance of the physician as a controlling agent in the use of vitamin products.

Mead Johnson & Company feel that vitamin therapy, like infant feeding, should be in the hands of the medical profession, and consequently refrain from exploiting vitamins to the public.

TULAREMIA TREATED WITH STREPTOMYCIN

Case Report No. 101

Robert Cawley, M.D. W. M. 43–9175

Benjamin Lafsky, M.D.

A seven year old white male was admitted to the Children's Hospital on May 13, 1947 because of a swelling in the left axillary region and fever. The patient, as stated by the mother, had been in good health until nine days prior to admission when he became rather irritable and complained of pain in the left axilla. The child has been re-vaccinated eight days prior to the onset of symptoms. The day following the vaccination was spent in the country near Culpepper, Virginia and two days later the mother noticed a tick in the left axilla and one in the right upper quadrant of the abdomen. These were removed with difficulty causing some bleeding. The mother at this time was not impressed with the tick bites and attributed the swelling of the left axilla to the vaccination. The symptoms of fever, irritability, pain, tenderness and swelling of the glands of the left axillary region became progressively worse. A physician was finally summoned who prescribed fluids, aspirin and sulfadiazine with no apparent benefit and finally, nine days after the onset of symptoms, the child was brought to the hospital.

The birth and developmental history were normal and the past illnesses included asthma and mumps. The child was immunized against pertussis, diphtheria and smallpox. The family history revealed that the father had died of kidney disease at the age of 33.

Physical examination revealed a fairly well developed and nourished white male appearing moderatly ill. The left axillary glands were enlarged, painful and tender with a small papule at the site of the tick bite. The remainder of the physical examination was negative except for a small erythematous area in the right upper quadrant of the abdomen, and a palpable spleen. The temperature was 100°F. Laboratory examination revealed 12.5 gms. % of hemoglobin, 4,200,000 erythrocytes, 9,600 leucocytes with a differential of 58% neutrophiles, 38% lymphocytes and 4% monocytes. Urinalysis was negative and a chest x-ray was normal. The temperature ranged between 99° and 103°F, the pulse rate between 90 and 130 with normal respirations.

Immediate therapy consisted of hot magnesium sulfate compresses to the left axilla and penicillin 20,000 units intramuscularly every three hours.

Surgical consultation on the 4th hospital day was obtained and continuation of the penicillin and magnesium sulfate compresses was advised.

The following day a punched-out ulcer about 1 cm. in diameter was noted at the site of the tick bite and at this time a diagnosis of tularemia was suspected. On the 6th day after admission to the hospital an agglutination test for tularemia was positive in dilutions of 1:20 through 1:20,480 and culture was subsequently positive on fresh blood glucose-cystine agar. In addition, the axillary lymph nodes were aspirated for guinea pig inoculation and B tularense was cultured from the guinea pig's spleen.

Streptomycin in doses of 150,000 units intramuscularly every three hours was immediately started. Seventy-two hours after initiation of antibiotic therapy the temperature had returned to normal and obvious clinical improvement and subsidence of constitutional symptoms were noted. Streptomycin was continued in doses of 150,000 units intramuscularly every 3 hours for 5 days and then decreased to 100,000 units intramuscularly every 3 hours for 6 days. The patient's condition continued to improve and he was discharged symptom free except for slightly enlarged lymph nodes in the left axilla 24 days after admission.

DISCUSSION

Tularemia, an infectious disease caused by the Bacterium tularense, is seen in practically all wild rodents, especially wild rabbits and hares. This disease is also seen in deers, coyotes, game birds, snakes, foxes, woodchucks, sheep, skunks, squirrels, oppossum, dogs, wood tick (Dermacenter Andersoni) and the common dog tick (Dermacentor Variabilis). Francis stresses the importance of ticks and tick bites in the transmission of the disease and states that the tick bite and contact with the wild rabbit account for 95% of human cases in the United States. The disease may also be contacted by eating uncooked infected meat and drinking infected water, and infection acquired in the laboratory is not infrequent, but is not communicable from man.

It is now recognized that the disease is world wide in its distribution. There are no significant differences in racial susceptibility and both sexes and all ages may readily acquire the disease. All ages are susceptible and permanent immunity follows recovery from an attack. The highest incidence of the disease is seen among those occupational groups who handle infected animal flesh (butchers, trappers etc.) and those exposed to ticks by nature of the geographic location.

It is convenient to classify tularemia into five different types depending upon the predominant expression of the disease process: (1) ulceroglandular type where the primary lesion is a papule of the skin, later becoming an ulcer with secondary enlargement of the regional lymph glands; (2) oculoglandular type in which the primary lesion is a conjunctivitis which is accompanied by enlargement of the regional lymph nodes; (3) glandular

type presenting the lymphadinitis without the primary lesion; (4) typhoid type in which there is no primary lesion nor is there glandular enlargement, but which presents a toxemia with a prolonged and debilitating pyrexia; (5) ingestion type characterized by an acute painful ulcerative pharyngitis or nasopharyngitis, enlargement of the submaxillary and cervical lymph nodes and gastro-intestinal manifestations. This clinical division is somewhat arbitrary and tends to fix the attention of the clinician upon the portal of entry of the infection rather than its systemic nature.

The incubation period is usually between three to five days but may vary between one to twenty-one days. The onset is usually acute with chills, fever, headache, nausea and vomiting and generalized body aches and pains. Weakness, loss of weight and sweats follow. A rash of a variable type may occur on any part of the body at any stage of the disease. The fever may be continuous or exhibit marked daily remission and the pulse rate is usually proportional to the fever. The spleen is frequently palpable and a moderate leucocytosis frequently occurs. The ulceroglandular type is by far the most common. A papule and later a punched-out ulcer forms at the site of the bite or injury and the regional lymph nodes become enlarged, painful and tender, and later suppuration may occur. In this form metastatic lesions may occur in the form of pneumonia, broncho-pneumonia, bronchitis, pleuritis, meningitis, peritonitis and cardiac involvement. In the oculoglandular type the primary seat of infection is the conjunctivae. This infection is usually transferred to the eyes by the hands while dressing rabbits or after crushing flies or ticks between the fingers. The symptoms of this type are conjunctivitis, pain, swollen lids, lacrimation, photophobia and the appearance of yellow papules on the palpebral conjunctivae which eventually break down into shallow yellow ulcers. The regional lymph glands are always enlarged (preauricular, parotid, submaxillary and anterior cervical) and suppuration may occur. The glandular type presents the lymphadenitis without the primary lesion. Here the infection may penetrate the skin without causing a local lesion, but causing enlargement of the regional lymph nodes. The typhoid type is the one usually seen in laboratory workers. Here there is neither a primary lesion nor an enlargement of the lymph nodes, but a general systemic infection with fever and prostration. Severe pulmonary or intestinal symptoms may occur. The ingestion type is seen following the ingestion of insufficiently cooked infected rabbit meat. The symptoms consist of fever, vomiting, diarrhea, abdominal pain with enlargement of the submaxillary and cervical lymph nodes.

Early diagnosis is extremely difficult and may be confused with other febrile illnesses such as influenza, psittacosis, atypical pneumonia, brucellosis, typhoid, tuberculosis, infectious mononucleosis, leukemias, lymphomas,

fungus infections of diverse types and various diseases accompanied by septicemia and bacteremia.

The macroscopic serum agglutination test is specific but is never positive during the first week of the illness and occasionally agglutinins may not appear in the serum until the third or fourth week of the illness. A titer of 1:20 is suspicious and 1:80 is diagnostic with significance being placed on a rising agglutining titer. Cross agglutinations with Brucella may occur and the highest titer usually indicates the primary disease. Agglutinins may persist indefinitely in the serum of patients. The intradermal test of Foshay in which a killed bacterial suspension is used as the test solution is said to be highly specific and positive in about 90% of patients during the first week. Like the agglutination test the skin test is positive for many years. Blood cultures may be positive during the stage of bacteremia or septicemia by direct innoculation of the patient's blood on fresh blood-glucose-cystine agar. Indirectly we may isolate the organism by first inoculating a guinea pig with the suspected human material followed by innoculation of culture media with the guinea pig tissue

Streptomycin approximates the ideal therapeutic agent for tularemia. It reduces secondary pyogenic infection of ulcers, greatly reduces the frequency of buboes and also reduces the resolution time of pulmonic exudates. The dosage has not yet been established but reports show that 1.0 gm. per day for 6 days seems to be adequate for the case of usual severity with or without tularemic pneumonia. The usual mode of administration was by intramuscular injection every three hours. All published reports to date are in agreement that streptomycin modified favorably the course of the disease usually promptly and often dramatically. The observed objective evidences of improvement were: lowered temperature, reduction in the diameter of buboes and restoration of mental clarity with relief from headache, severe prostration, mental depression and lessened pain in primary lesions and in buboes.

It is not known at present whether streptomycin treatment in tularemia will have any effect on the duration of persistence of serum agglutinins. It is also interesting to note that streptomycin given early in the disease might prevent the development of acquired immunity and expose the individual to the danger of reinfection.

REFERENCES

1. Toshay, L.: Treatment of Tularemia with Streptomycin. Am. J. Med., **2:** 467–73, 1947.
2. Hunt, John S.: Pleuropulmonary Tularemia. Observation on 12 Cases Treated with Streptomycin. Ann. of Int. Med., **26:** 263, Feb., 1947.
3. Pullen, Roscoe L., and Stewart, Byron M.: Tularemia. New Orleans Med. and Surg. Jour., **98:** 126, September, 1945.

4. Pullen, Roscoe L., and Stewart, Byron M.: Tularemia, Analysis of 225 Cases. Jour. of the Amer. Med. Assn., **129:** 495, October 13, 1945.
5. Moore, Francis D., Sawyer, Carl S., and Blount, S. Gilbert, Jr.: Tularemia in New England; a Review of Eighteen Cases with the Report of Two Additional Cases. New Eng. Jour. of Med., **231:** 169, Aug. 3, 1944.
6. Yater: Fundamentals of Int. Medicine, 639–642.
7. Heather, Arthur J., and Scott, Elvyn G.: Tularemia Treated with Streptomycin. Del. State Med. Jour., **18:** 148, July, 1946.
8. Witherington, J. B.: Tularemia Treated with Streptomycin Sulfate. Memphis Med. Jour., **21:** 139, Sept., 1946.
9. Aagaard, George N.: Involvement of the Heart in Tularemia. Report of Two Cases. Minnesota Med., **27:** 115, February, 1944.
10. Howe, Calderon, Coriell, Lewis L., Bookwalter, H. L., and Ellingson, H. V.: Streptomycin Treatment in Tularemia. Jour. of the Amer. Med. Assn., **132:** 195, Sept. 28, 1946.
11. Brenneman's Practice of Pediatrics, McQuarrie. Vol. II, Chap. 29, pp. 1–11.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by E. Clarence Rice, M.D.

By Invitation Preston A. McLendon, M.D. E. R. 40–426

A seven month old white female was admitted to the Children's Hospital on January 16th because of fever of 106°F, lethargy and convulsions. The child had a cold and cough for approximately two weeks prior to admission but no episodes of vomiting or diarrhea.

The birth history revealed a normal labor and delivery. The child weighed six pounds and eight ounces at birth. There was no history of neonatal cyanosis, jaundice or convulsions. The family history was noncontributary.

Physical examination revealed an acutely ill infant, breathing with difficulty and appearing listless and drowsy. The fontanel was patent but not bulging or pulsating. Both eyes and ears contained a purulent discharge. Fine moist râles were heard at the right base but there was no dullness. The abdomen was soft and doughy. The liver extended one finger's breadth below the ribs and the spleen was not palpated. The extremities revealed no gross abnormalities. Neurological examination revealed a suggestive stiffness of the neck but no Brudzinski sign or other abnormalities.

Shortly after admission a spinal tap was done; the fluid obtained was blood-tinged and after centrifuging was found to be xanthrochromic in color. Hemogram revealed 5.7 gms. % of hemoglobin, 2,200,000 erythrocytes and 15,500 leucocytes, with 41% neutrophiles (36% bands and 5% stab) and 59% lymphocytes. The urinalysis showed no sugar or acetone, 40 mgm. % of albumin, a few epithelial cells, many leucocytes and an occasional erythrocyte. CO_2 combining power was 46 volumes percent. Tuberculin test (O.T. 1/1000) was negative. X-ray examination of the chest revealed a small circumscribed area of opacity involving the right base, having the appearance of an early or resolving inflammatory process. The heart and thymus appeared normal.

In the hospital the child was given sulfonamides together with intravenous crystalloid fluids and a blood transfusion; following this, slight improvement was noted during the first 48 hours, but on the following day the child went into coma and expired 4 days after hospitalization.

DISCUSSION

P. A. McLendon, M.D.: This sketchy history of a presumably normal child with a normal birth and infant history suggests an acute overwhelming

infection. When preceded by a short history of a "cold" and cough the respiratory system is first suspected. The admitting symptoms could result from a pneumonia with a generalized infection involving the ears, pharynx and bronchi. On physical examination the above interpretation was borne out by evidence of a purulent otitis media and râles at the right base.

The most frequent causes of convulsion in infants are: acute respiratory infections including tonsillitis, meningeal infections, urinary infections and gastro-intestinal infections. Lethargy would be a coincident symptom in any one of these. The possibility of a meningeal infection cannot be ruled out since there is evidence of a mild degree of neck stiffness. The fontanel is not bulging but that need not be present in a patient so young and one ill for such a short time. The spinal fluid finding is of no help either way. Urinary infection complicating the preceding "cold" is a good probability especially as there is a moderate amount of albumin and many leucocytes and a few erythrocytes reported. This may be an acute hematogenous infection or the recurrence of a previous attack on an anomalous basis. Anomaly of the genito-urinary system is frequent, and often overlooked.

"Difficulty in breathing" is given as a prominent objective symtom. This might be due to the very high temperature and the need for increased oxygenation. Acidosis is ruled out by the carbon dioxide combining power of 46 volumes percent. Pulmonary infection would of course be the plausible explanation and this is borne out by physical findings in the right base corroborated by X-ray. The blood count is of little value since infections in children (particularly with an abrupt onset) cause variable responses unlike those encountered in adults. They are generally of questionable value when considered individually.

Tuberculosis involving the lung would probably be inconsistent with the negative tuberculin: however, such an infection need not necessarily give a positive reaction; in fact, in sudden overwhelming tuberculous infections, it is not unusual to find the Mantoux negative.

In summary my impressions would be: 1. Pulmonary and kidney infection with general septicemia associated with otitis media, 2. Brain abscess with septicemia.

NECROPSY FINDINGS

E. Clarence Rice, M.D.: Nearly clear, pink fluid was obtained from the cisterna magna, which after centrifuging was found to be xanthochromic. Examination of the skull revealed no abnormal findings in the venous sinuses or the mastoid air cells. The convolutions of the brain and its surface were darkened over the left fronto-parietal and temporal lobes

and the right parietal lobe. On section these lobes were found to be soft and brownish in color due to disintegration, the left frontal lobe being almost completely destroyed. Both anterior cerebral and the left middle cerebral arteries were thrombosed and likewise the veins over the affected areas. Microscopic examination of the brain revealed thromboses of both arteries and veins with evidence of hemorrhage and degeneration. In most places the leucocytic reaction was not intense and only in the region of the meninges were any number of polymorphonuclears present. Elsewhere moderate numbers of lymphocytes were observed. Evidence of hemorrhage and various stages of cerebral degeneration were found. Arteries showed destruction of most of the coats except the adventitia.

The lungs were atelectatic in some areas, emphysematous in others. The heart muscle was flabby and microscopically the fibers gave evidence of degenerative changes. The liver showed evidence of marked fatty metamorphosis with some thickening of the portal veins. The kidneys presented no distinctive gross changes but microscopically exhibited congestion with areas of tubular degeneration. Large areas of leucocytic infiltration about the tubules and to a lesser extent around the glomeruli were present.

Heart's blood culture was sterile, that from the softened area in the brain gave a growth of large gram positive cocci and bacilli.

The pathological diagnoses were:

1. Cerebral degeneration following thromboses of both anterior cerebral and left middle cerebral arteries. Thrombosis of cerebral veins draining the above areas.
2. Pulmonary atelectasis and emphysema.
3. Toxic myocardial degeneration.
4. Fatty metamorphosis of the liver.
5. Acute pyelonephritis.

The findings appear to be accounted for by a debilitating illness and a rather prolonged series of infections. Purulent exudates were noted in the eyes and ears and pus was found in the urine which was due to an acute pyelonephritis. There had been a history of a respiratory infection two weeks prior to admission. I am inclined to believe that the organisms recovered from the lesions in the brain were probably contaminants or terminal invaders as the microscopic examination does not indicate an abscess. The fact that vascular changes were noted in the liver and that the heart muscle revealed toxic degeneration would support the presumption that the vascular changes were due to degenerative changes within their walls due to certain bacterial toxins elaborated elsewhere. This with the anemia and the probable reduced flow of blood through the vessels might have aided in their occlusion.

Somewhat similar cases have been reported by Rollerson and Wiesel.

REFERENCES

1. Rollerson, J. D.: Three Cases of Hemiplegia following Scarlet Fever. Arch. Neurol. & Psychiat., **6:** 530, 1908.
2. Rollerson, J. D.: Transient Hemiplegia in Diphtheria. Rev. Neurol. & Psychiat., **14:** 145, 1916.
3. Wiesel, J.: Die Erkraukungen Arterieller Geffasse im Verlaufe Akuter Infektionen. B. Heilk. Abt. fur. path. anat., **27:** 69, 1907.